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Effect of vasopressin antagonist on water excretion in inferior vena cava constriction

SAN-E ISHIKAWA, TOSHIKAZU SAITO, KOJI OKADA, KUMIKO TSUTSUI, and TAKESHI KUZUYA

Division of Endocrinology and Metabolism, Department of Medicine, Jichi Medical School, Minamikawachi-machi, Tochigi 329-04, Japan

Effect of vasopressin antagonist on water excretion in inferior vena cava constriction. Elevated levels of plasma arginine vasopressin (AVP) have been suggested to impair water excretion in congestive heart failure. In the present study, to determine a role for AVP in the impaired water excretion in rats with the inferior vena cava constriction (IVC), two AVP antagonists were used in the IVC rats at the proximal portion of the hepatic vein under the diaphragm and in sham-operated (control) rats. After surgery, 48 hrs were allowed before the experiments were started. A mean cardiac index of 260.0 ± 12.3 ml/min/kg in the IVC rats was significantly lower than that in the control rats, 323.6 ± 13.2 ml/min/kg ($P < 0.01$). The rats were given an antidiuretic antagonist, [1-(β-mercapto-β, β-cyclopentamethylenepropionic acid), 2-(O-ethyl)-D-tyrosine, 4-valine] AVP (30 μg/kg) or the antagonist vehicle, i.p., and 20 min later they were administered 30 ml/kg of water orally. Minimal urinary osmolality (Uosm) in the IVC rats receiving the vehicle was significantly greater than the control rats (292.7 ± 53.1 vs. 97.8 ± 10.6 mOsm/kg H_2O, $P < 0.01$). The administration of the antidiuretic antagonist in the IVC rats decreased minimal Uosm to 90.0 ± 3.6 mOsm/kg H_2O. This value was significantly lower than the vehicle rats ($P < 0.01$), and was a comparable level to minimal Uosm of 82.1 ± 3.7 mOsm/kg H_2O in the control rats receiving the antidiuretic antagonist. The IVC rats excreted 51.4 ± 5.9% of the water load in three hr, a value significantly less than that excreted by the control rats, 95.1 ± 6.0% ($P < 0.01$). When treated with the antidiuretic antagonist, the percent of water load excreted increased to 143.7 ± 9.4% in the IVC rats. The efficacy of the antidiuretic antagonist was associated with nonsuppressible plasma AVP levels. The plasma AVP level of 2.1 ± 0.6 pg/ml was not sufficiently suppressed in the IVC rats by the administration of water, which induced hypoosmolality. In contrast, in the control rats plasma AVP was decreased to 0.7 ± 0.2 pg/ml in the same situation. However, the elevated AVP did not contribute to the maintenance of blood pressure since the vasopressor antagonist, [1-(β-mercapto-β, β-cyclopentamethylenepropionic acid), 2-(O-methyl)-tyrosine] AVP, did not affect mean arterial pressure. These results therefore indicate that the non-osmotic release of AVP is inappropriately increased to impair renal water excretion in the IVC rats and the biological efficacy of the antidiuretic antagonist in such a state is expected.

Clinical and laboratory experiments have demonstrated that low output cardiac failure is associated with impaired water excretion [1–3]. Persistent plasma levels of radioimmunoassayable arginine vasopressin (AVP) were shown in man and animals by other laboratories, in spite of levels of hypoosmolality which should suppress the osmotic release of AVP to undetectable levels [4, 5]. Reversal of water retention by using a specific inhibitor of AVP would provide quantitative and conclusive evidence for a role of AVP in water retention in a model, which may stimulate some features of low output cardiac failure. This is important since intrarenal factors may also contribute to the impaired water excretion [6, 7]. Such a study is now possible because Manning and Sawyer have developed novel antagonists of the antidiuretic effect of AVP [8–12]. We have already reported the reversal of the impaired water excretion in glucocorticoid and mineralocorticoid deficiency with a specific and potent antagonist to the antidiuretic effect of AVP [13].

In the present study, we determined whether AVP is important in the pathogenesis of the impaired water excretion in rats with the inferior vena cava constriction (IVC) by using the antagonist to the antidiuretic effect of AVP. Also, whether or not AVP contributes circulatory homeostasis in the IVC rats was examined with the use of a specific antagonist to the vascular effect of AVP.

Methods

Male Sprague–Dawley rats weighing 230 to 270 g were used in the present experiments. Under ether anesthesia the abdomen was opened via a midline incision. A portion of the abdominal inferior vena cava between the take-off of the hepatic vein and the diaphragm was carefully dissected out from the surrounding tissues and then tied together with three pieces of polyethylene (PE-100) tubing (Clay–Adams, Division of Becton, Dickinson & Co., Parsippany, New Jersey, USA) by silk thread. The polyethylene tubes were then removed to produce the constriction of the abdominal inferior vena cava (IVC). Sham-operated rats were prepared in the same manner but without the constriction. After surgery the animals were allowed free access to water and food for 48 hrs and were subjected to the following experiments.

Systemic hemodynamic studies

To determine changes in systemic hemodynamics of the IVC rats, the two groups of animals were studied using a radioactive microsphere technique [14]. Briefly, after induction of anesthesia with ether, polyethylene catheters (PE-50, Clay–Adams) were inserted into the femoral artery and vein. A third catheter of tapered PE-350 tubing (Clay–Adams) was advanced retrograde through the right carotid artery into the left ventricle for microspheres injection. Ventricular placement was confirmed by the pressure–wave tracing at the time of catheterization and

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by direct observation at the end of each experiment. The rats were then placed in restraining cages (Shinnihon Sangyo Co., Tochigi, Japan), and allowed to awaken. At least two hrs passed after the animals had awakened before the experiments were started to determine cardiac output and renal blood flow by a radioactive microsphere technique. The microspheres used were 15.9 ± 0.3 μ in diameter and were labelled with ^{51}Cr (specific activity, 11.42 mCi/g, New England Nuclear, Boston, Massachusetts, USA). Mean arterial pressure (MAP) was measured. For each experiment, 0.6 ml of a 0.9% NaCl solution containing 1.4×10^5 microspheres was injected through the carotid line in approximately five sec. Thereafter, the catheter was flushed with 0.4 ml of 0.9% NaCl. The microspheres were prepared as follows just before the injection. The radioactivity of the solution containing ^{51}Cr-microspheres was counted in a Aloka Gamma Counter (Model ARC-600, Tokyo, Japan). The solution was vigorously agitated using a vortex mixer for at least five min just prior to injection. Immediately prior to the injection of the microspheres, the arterial blood collection was started from the femoral artery line at a rate of 1 ml/min for two min (Harvard pump, Harvard Apparatus Co., Dover, Massachusetts). The animals were killed by an overdose of anesthetic. Collected blood samples, the femoral artery line, the injection syringes, and the carotid artery line were transferred into separate plastic tubes to count the radioactivity. The heart and the kidneys were also removed, weighed and counted for radioactivity. Cardiac index, total peripheral vascular resistance, renal blood flow and vascular resistance were calculated as follows:

$$\text{Cardiac index (ml/min/kg)} = \frac{\text{Injected microspheres (cpm)}}{\text{Femoral blood (cpm)}} \times \frac{\text{Rate of collection of femoral arterial blood (ml/min)}}{\text{Body weight (kg)}}$$

$$\text{Total peripheral vascular resistance (mm Hg/ml/min/kg)} = \frac{\text{Mean arterial pressure (mm Hg)}}{\text{Cardiac index (ml/min/kg)}}$$

$$\text{Renal blood flow (ml/min/g)} = \frac{\text{Kidney counts (cpm)}}{\text{Femoral blood (cpm)}} \times \frac{\text{Rate of collection of femoral arterial blood (ml/min)}}{\text{Kidney weight (g)}}$$

$$\text{Renal vascular resistance (mm Hg/ml/min/g)} = \frac{\text{Mean arterial pressure (mm Hg)}}{\text{Renal blood flow (ml/min/g)}}$$

Effect of inferior vena cava constriction on plasma AVP and plasma osmolality

To determine the role of plasma AVP in water retention in IVC rats, these experiments were performed in IVC rats and in sham–operated rats. The animals were allowed free access to water and food after operation. Forty-eight hrs later the animals were decapitated by guillotine to collect blood. Other groups of rats were given de-ionized water (30 ml/kg) orally by a gastric tube under transient, light ether anesthesia, allowed to awaken, and then blood was taken by decapitation 60 min later after the oral water load. This time was chosen since our experiments showed the maximal urine flow and the minimal urinary osmolality (Uosm) occurred approximately 40 to 80 min after the oral water load. All blood samples were taken in heparinized tubes on ice. These samples were centrifuged at 4°C and 3,000 rpm for 15 min. The plasma was decanted into other tubes and frozen at −20°C until the time of assay.

Plasma AVP was measured by radioimmunoassay using AVP antiserum [15]. The samples were extracted by the Sep-pak method. Sep-pak cartridges (Waters Associates, Milford, Massachusetts, USA) were initially washed twice with 5 ml of methanol, and then rinsed with 12 ml of distilled water. 0.5 ml of plasma with 0.5 ml of 0.1 N HCl was applied into a Sep-pak column, followed by washing with 10 ml of 4% acetic acid. The samples were eluted with 1.5 ml of methanol and then dried under a stream of nitrogen at room temperature. The precipitations were dissolved in 0.8 ml of 0.1 M phosphate buffer (0.1 M phosphate buffer, 0.01% NaN_3, 0.1% bovine serum albumin, pH 7.4) and used to measure AVP by radioimmunoassay. The lower limit of detection of the standard curves was 0.15 pg/ml. A synthetic AVP (grade VI, designated activity of 367 IU/mg, Sigma, St. Louis, Missouri, USA) was used for the standard curves. Intra- and inter-assay coefficients of variation are less than 10%. Lysine vasopressin show 100% immunoreactivity when compared with AVP. 1-Deamino-8-D-AVP show 1.3% crossreactivity with the AVP antiserum. However, oxytocin, arginine vasotocin and pressinoic acid crossreact by less than 0.1% with the AVP antiserum [15].

Other groups of IVC and sham–operated rats prepared in the same manner were used to measure plasma osmolality (Posm). 1.2 ml of blood was taken from tail artery and vein under ether anesthesia. Posm was measured by freezing–point depression (Model 3R, Advanced Instruments, Inc., Needham Heights, Massachusetts, USA).

Effect of the antidiuretic antagonist on renal water excretion

Acute oral water loads were carried out in IVC and sham–operated rats to evaluate the effect of low cardiac output on renal water excretion. The experiments were started two hrs after removal of food and water in the following manner: the rats were administered intraperitoneally 30 μg/kg of [1-(β-mercapto-β, β-cyclopentamethylenepropionic acid), 2-(O-ethyl) D-tyrosine, 4-valine] AVP, $d(CH_2)_5$D-Tyr(Et)VAVP [9], or the vehicle, 2.5×10^{-7} M acetic acid and 0.9% saline, and 20 min later they were given 30 ml/kg of deionized water by a gastric tube under light ether anesthesia. The animals were then placed in individual metabolic cages (Natsume Inc., Tokyo, Japan) and allowed to awaken. Spontaneously voided urine samples were then collected at 20 min intervals for three hrs [13]. The final urine samples were obtained by abdominal massage at the end of experiments. Urine volume and Uosm were measured and percent of water load excreted and minimal Uosm were recorded. Uosm was measured by freezing–point depression.

Before the above experiment, the following study was performed to determine what dose of $d(CH_2)_5$D-Tyr(Et)VAVP was enough to block the antidiuretic action of endogenous AVP. $d(CH_2)_5$D-Tyr(Et)VAVP was administered intraperitoneally into normal hydrated Sprague–Dawley rats. Spontaneously voided urine samples were collected at 30 min intervals for three hrs. The following data show the minimal Uosm (mOsm/kg H_2O, mean ± SEM) with the dose of the AVP antagonist shown in bracket: 869.8 ± 224.1 (vehicle); 423.6 ±

33.0 (5 μg/kg body wt); 134.6 ± 9.9 (15 μg/kg body wt); and 98.2 ± 11.2 (30 μg/kg body wt). Each group has five observations.

Effect of the vasopressor antagonist on mean arterial pressure

Animals were used 48 hrs after the IVC operation. After induction of anesthesia with ether, a catheter (PE-50, Clay–Adams) was inserted into the left femoral vein for drug administration. Another catheter was inserted into the left femoral artery for monitoring blood pressure (Pressure transducer, Model PAS-101, Star Medical Co., Tokyo, Japan; and Model 056 Recorder, Hitachi Electric Co., Tokyo, Japan). The rats then were placed in a restrainer and allowed to awaken. At least two hrs after catheter insertion was allowed before the experiments were started. The baseline mean arterial pressure (MAP) was monitored until stable for at least 30 min. Thereafter, the vasopressor antagonist, [1-(β-mercapto-β, β-cyclopentamethylenepropionic acid), 2-(O-methyl)-tyrosine] AVP, $d(CH_2)_5Tyr(Me)AVP$ (5 μg/kg body weight) or the vehicle (0.9% saline containing 2.5×10^{-7} M acetic acid) was injected intravenously in a volume of 0.4 ml [16, 17], and then MAP was monitored for the next 60 min. In all experiments the maximal stable decrement in MAP was used for statistical analysis.

Effect of the antidiuretic antagonist on GFR

Experiments were also performed to ascertain whether the antidiuretic antagonist, $d(CH_2)_5D$-Tyr(Et)VAVP affected glomerular filtration rate (GFR) in the IVC rats. After induction of anesthesia with ether, catheters (PE-50) were inserted into the external jugular vein and carotid artery. A suprapubic catheter (PE-100) was inserted into the urinary bladder. The rats then were placed in restraining cages and allowed to awaken. At least two hrs passed after the animals had awakened before the experiments were started. The animals were infused with 0.9% saline containing ^{3}H-methoxy-inulin (specific activity, 345 mCi/g, New England Nuclear, Boston, Massachusetts, USA) at a rate of 7 ml/hr (7 μCi/hr) (Harvard pump) [18]. After 60 min, three, 10 min urine collections were made and then the antidiuretic antagonist (30 μg/kg) was administered intraperitoneally. Urine samples were then taken at 10 min intervals for 60 min. A blood sample was taken from the carotid artery line before the administration of the antidiuretic antagonist and at the end of the experiments. The concentrations of ^{3}H-methoxy-inulin were determined using Aloka LSC-671 Liquid Scintillation Spectrometer (Tokyo, Japan). Inulin clearance was calculated as an index of GFR [13].

Measurements of tissue solute contents

Solute contents of whole inner medulla (papilla) of the kidneys were determined by the method of Appelboom et al [19]. In these studies, the animals were killed after 48 hrs of the IVC operation. The abdomen was opened and both kidneys were removed rapidly and placed in an ice bath. The kidneys were cut along their longitudinal axis and the inner medulla was dissected free, weighed and freezed in liquid nitrogen. One sample was for the determination of osmolality, sodium, potassium and urea, while the other was dried to constant weight for determination of tissue water content. Osmolality was measured by freezing-point depression. Sodium and potassium contents were determined by flame photometry (Instrumentation Laboratories, Cidra, Puerto Rico), while urea was measured by urea nitrogen assay kit (Wako Junyaku Co., Tokyo, Japan). The inner medullary tissue osmolality was finally calculated from the observed osmolality. Also, this was confirmed by calculating from sodium, potassium and urea contents [20].

Statistics

All values were compared between the groups by the unpaired Student's *t*-test. Alterations in MAP within groups were compared by the paired Student's *t*-test. A P value less than 0.05 was considered significant.

Results

Systemic hemodynamic parameters in the IVC and the control, sham–operated rats are shown in Table 1. MAP was not different between the groups. A cardiac index of 260.0 ± 12.3 ml/min/kg in the IVC rats was significantly less than that of 323.6 ± 13.2 ml/min/kg in the sham–operated rats. In contrast, peripheral vascular resistance was significantly greater in the IVC rats than the sham–operated rats. Renal blood flow was significantly lower in the IVC rats than the sham–operated rats. However, there was no significant difference in renal vascular resistance between the two groups. Heart weight was significantly lighter in the IVC rats than the sham–operated rats.

Figure 1 shows Posm in the IVC rats and sham–operated rats 60 min after an acute oral water load. Plasma osmolality was decreased to 275.6 ± 1.0 mOsm/kg H_2O in the IVC rats, a value significantly less than 280.1 ± 1.3 mOsm/kg H_2O of the sham–operated rats. When the animals were allowed free access to water and food, Posm was lower, but not significantly different in the IVC rats as compared to the sham–operated rats (283.3 ± 3.3 vs. 287.6 ± 2.2 mOsm/kg H_2O, $N = 8$, NS).

Figure 2 shows plasma AVP levels during water intake ad libitum (A) and 60 min after an acute oral water load (B). When the animals were allowed free access to water and food, plasma AVP was significantly higher in the IVC rats than the sham–operated rats. Sixty min after an acute water load, plasma AVP in the sham–operated rats was reduced to 0.7 ± 0.2 pg/ml. In the IVC rats, however, the plasma AVP level of 2.1 ± 0.6 pg/ml was not sufficiently suppressed by the administration of water.

Figure 3 shows the effects of the antidiuretic antagonist vs. the antagonist vehicle on minimal Uosm in the IVC and sham–operated rats. In the sham–operated rats there was little difference in minimal Uosm between the vehicle and the antidiuretic antagonist rats (97.9 ± 10.6 vs. 82.1 ± 3.7 mOsm/kg H_2O, NS). The minimal Uosm in the IVC rats receiving the vehicle was markedly higher than that in the sham–operated rats ($P < 0.01$). The difference in the minimal Uosm in the IVC rats between the vehicle and the antidiuretic antagonist was quite evident (292.7 ± 53.1 vs. 90.0 ± 3.6 mOsm/kg H_2O, $P < 0.01$). This result demonstrates that endogenous AVP is an important factor in the defect in urinary dilution in the IVC rats. It is not evident that AVP-independent defect in urinary dilution persists as minimal Uosm was not different between the IVC and sham–operated rats in the presence of the antidiuretic antagonist (90.0 ± 3.6 vs. 82.1 ± 3.7 mOsm/kg H_2O, NS). The difference in the percent of water excreted in the IVC rats between the vehicle and the antidiuretic antagonist was 51.4 ±

Table 1. Systemic hemodynamic parameters in rats with inferior vena cava constriction and sham–operated rats.

	N	Mean arterial pressure *mm Hg*	Cardiac index *ml/min/kg*	Peripheral vascular resistance *mm Hg/ml/min/kg*	Renal blood flow *ml/min/g*	Renal vascular resistance *mm Hg/ml/min/g*	Heart weight *g/kg*
IVC rats	8	102.6 ± 3.2	260.0 ± 12.3	0.397 ± 0.019	4.9 ± 0.4	21.67 ± 1.76	3.48 ± 0.13
Sham–operated rats	8	105.3 ± 1.4	323.6 ± 13.2	0.328 ± 0.015	6.2 ± 0.4	17.53 ± 1.11	4.23 ± 0.16
P value		NS	<0.01	<0.05	<0.05	NS	<0.01

Values are mean ± SEM.

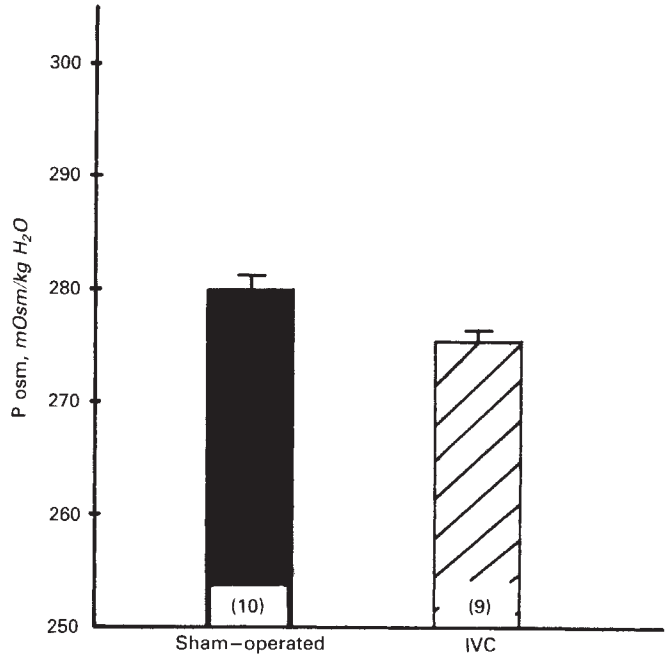

Fig. 1. *Plasma osmolality 60 min after an acute oral water load in the rats with inferior vena cava constriction and the sham–operated rats.* Values are mean ± SEM, $P < 0.05$.

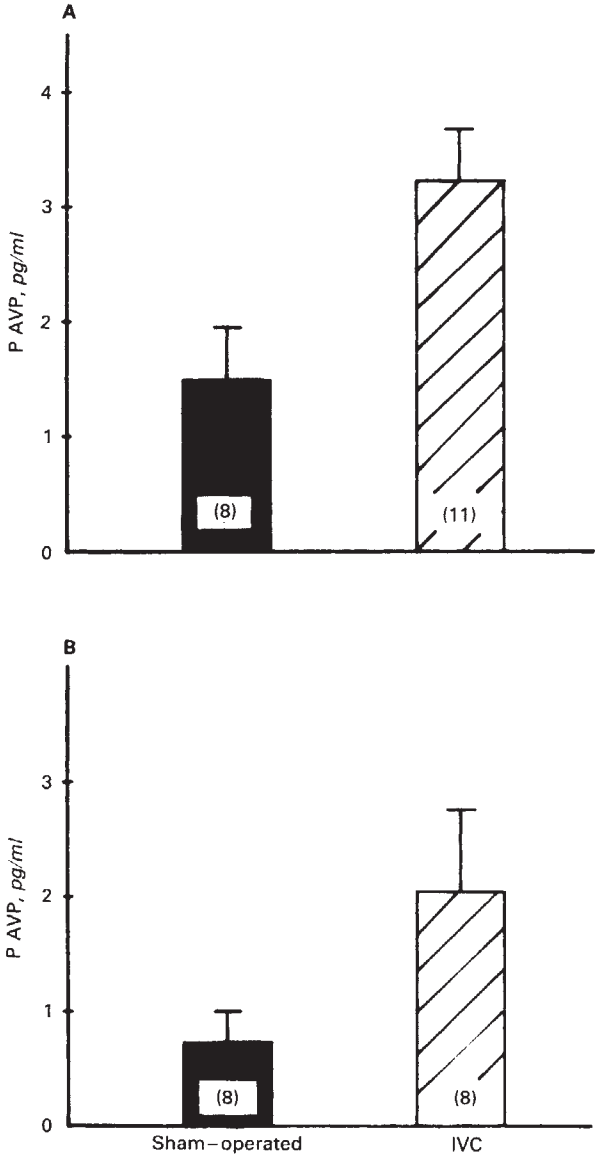

Fig. 2. *Plasma AVP levels during water intake ad libitum* (**A**) *and 60 min after an acute oral water load* (**B**) *in the rats with inferior vena cava constriction and the sham–operated rats.* Values are mean ± SEM, $P < 0.05$.

5.9% vs. 143.7 ± 9.4% ($P < 0.01$). Also, similar results were obtained in the sham–operated rats (95.1 ± 6.0% vs. 176.1 ± 7.5%, $P < 0.01$). Effect of the antidiuretic antagonist vs. the vehicle on renal solute excretion is shown by using UosmV. UosmV were 12.3 ± 1.0 and 11.0 ± 1.0 μOsm/min in the IVC rats receiving the vehicle and the antidiuretic antagonist, respectively. Similarly, the sham–operated rats receiving the vehicle and the antidiuretic antagonist had a UosmV of 10.8 ± 0.8 and 11.7 ± 0.8 μOsm/min, respectively. There was no difference in solute excretion among any group.

Table 2 shows the effect of the antidiuretic antagonist on GFR in IVC rats. The value of GFR in the IVC rats is slightly but not significantly less when compared with the sham–operated rats. Also, there was no significant difference in GFR between the presence and absence of the antidiuretic antagonist. Inner medullary solute contents were 1009.7 ± 148.2 and 1196.7 ± 86.0 mOsm/kg H_2O in the IVC ($N = 5$) and the sham–operated rats ($N = 5$) respectively, which was no statistically significant between the two groups.

The MAP responses to either the vasopressor antagonist or the vehicle are depicted in Figure 4. Baseline MAP was not different among the four groups of the IVC and sham–operated rats. There were no alterations in MAP in response to either the vasopressor antagonist or the vehicle in either IVC or sham–operated animals.

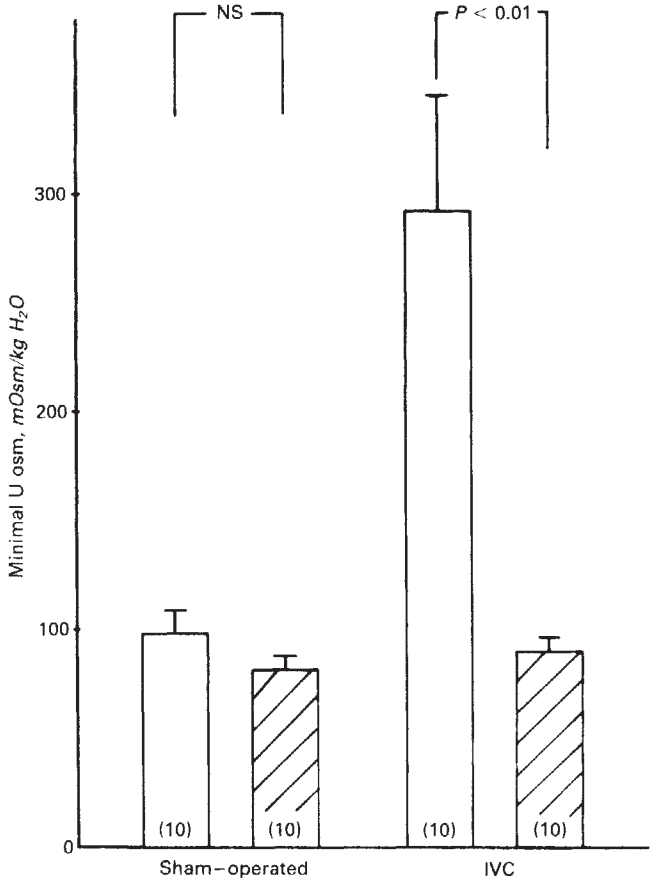

Fig. 3. *Effects of the antidiuretic antagonist (□) vs. the antagonist vehicle (□) on minimal Uosm in the rats with inferior vena cava constriction and the sham-operated rats.* Values are mean ± SEM.

Discussion

Acute constriction of the thoracic inferior vena cava in dogs decreases cardiac output and increases total peripheral vascular resistance [3, 21]. Anderson and his associates demonstrated that in this dog model, low cardiac output causes impaired water excretion which is associated with the elevated levels of plasma AVP [3]. The maneuver which causes constriction of the subdiaphragmatic portion of the inferior vena cava proximal to the hepatic vein can reproduce this experimental model of low cardiac output. The cardiac output was significantly lower in the experimental group than the control, sham-operated rats. In contrast to acute constriction of the thoracic inferior vena cava in dogs which decreases MAP, the MAP remained unchanged in the IVC rats 48 hrs after the constriction. The present model of rats is therefore useful to evaluate the pathogenesis of impaired water excretion associated with low cardiac output.

Congestive heart failure has been known to be associated with impaired water excretion in both man and animals [1–5]. In recent years the suggested mechanisms for this impaired water excretion have included persistent release of AVP in the presence of hypoosmolality [3–5] and intrarenal factors [6, 7]. The present results provide strong confirmatory evidence for a role of plasma AVP in the impaired water excretion associated with this model of low cardiac output. The radioimmunoassayable plasma levels of AVP was increased significantly in the IVC rats, despite a relatively lower Posm than the sham-operated rats. Also, nonsuppressible radioimmunoassayable levels of plasma AVP were demonstrable in the presence of hypoosmolality in the IVC rats during an acute oral water load, that suppresses plasma AVP in normal animals to less than 1 pg/ml. Thus, the elevation of plasma AVP should be related to non-osmotic stimulus, that is, the diminution in cardiac output, as suggested by the previous studies [3, 22, 23]. It has heretofore been believed possible that the elevated plasma AVP was not exerting a physiological effect on renal water excretion. The administration of the antidiuretic antagonist, $d(CH_2)_5$D-Tyr(Et)VAVP, resulted in a marked improvement in water excretion in the IVC rats. In the presence of the antidiuretic antagonist, the minimal Uosm in the IVC rats was at a comparable level to that in the control rats and the percent of water excreted exceeded over 100%. The latter was due probably to the sustained effect of the antidiuretic antagonist during the acute water load, because in its absence maximal urine flow rate occurs between 40 and 80 min, followed by a gradual decrease. Similar results were obtained in the control rats; the minimal Uosm was not different in the presence or absence of the antidiuretic antagonist, but the percent of water excreted increased markedly in its presence.

A series of the antidiuretic antagonists, developed by Manning, Sawyer and their associates [8–12], exert potent inhibitory effects on the antidiuretic action of AVP. $d(CH_2)_5$D-Tyr(Et)VAVP used in this study has a pA_2 value of 7.81 [9], which

Table 2. Effect of the antidiuretic antagonist $d(CH_2)_5$D-Tyr(Et)VAVP on glomerular filtration rate (GFR) in rats with inferior vena cava constriction.

	GFR (ml/min)		
	Basal	AVP Antagonist	*P* value
IVC rats, $N = 6$	2.5 ± 0.2	2.4 ± 0.2	NS
Sham-operated rats $N = 6$	2.8 ± 0.2	2.9 ± 0.3	NS
P value (IVC vs. Sham)	NS	NS	

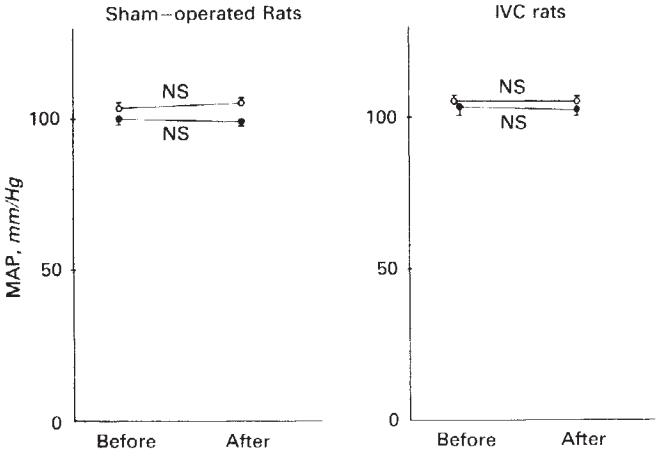

Fig. 4. *Effect of the inferior vena cava constriction on mean arterial pressure (MAP) response to the vasopressor antagonist in the conscious rats.* Symbols are: ●, group with vehicle; ○, group with the vasopressor antagonist, $d(CH_2)_5$Tyr(Me)AVP (5 μg/kg body wt, i.v.). Values are mean ± SEM. Each group has ten observations.

is almost twice as potent as [1-β-mercapto-β, β-cyclopentamethylenepropionic acid), 2-(O-ethyl)-tyrosine, 4-valine] AVP used in our previous works [8, 13, 24]. A dose of $d(CH_2)_5$D-Tyr(Et)VAVP with 30 μg/kg intraperitoneally is sufficient to inhibit the antidiuretic action of AVP. The improvement in water excretion is not due to an increase in renal solute excretion and GFR.

In the present study there is no evidence for a role of AVP-independent factors in the impaired water excretion in the IVC rats. Pretreatment with the antidiuretic antagonist decreased minimal Uosm to 90.0 ± 3.6 mOsm/kg H_2O, which is not statistically different from the control rats treated with the antidiuretic antagonist. Also, there was no significant difference in GFR, renal solute excretion and inner medullary tissue solute contents between the IVC rats and the control rats. The finding of no decrease in GFR in IVC rats was compatible with that in dog during an acute constriction of thoracic inferior vena cava [21]. The present study, therefore, does not suggest an intrarenal factor in the impairment in water excretion.

As described above, we demonstrate the elevated level of plasma AVP, which is an important factor in water retention in the model of low cardiac output, and the biological efficacy of the antidiuretic antagonist in such a state. However, the MAP in the IVC rats was comparable to those in the control rats, and the vasopressor antagonist did not affect MAP in the IVC rats, thus indicating that endogenous AVP does not exert a vascular effect to maintain blood pressure. This finding may be explicable on the basis of the plasma AVP levels, since plasma AVP levels of more than 20 pg/ml is necessary to influence blood pressure in normal rats, even though in pathological state more than 10 pg/ml of plasma AVP levels were suggested [14, 17, 25]. Similar results were obtained in high output cardiac failure with arteriovenous fistula from another laboratory [26]. They did not report an effect of an antidiuretic antagonist in the pathological state of water retention in their rat model.

In summary, the use of a potent antagonist to the antidiuretic action of AVP demonstrated a role for plasma AVP in the pathological state of water retention associated with low cardiac output. Non-osmotic release of AVP does not appear to contribute to circulatory homeostasis in this circumstance [27]. The present study therefore indicates that the non-osmotic, baroreceptor-mediated release of AVP is inappropriately increased in the IVC rats, and that the future use of the antidiuretic antagonist may be expected to produce clinical improvement of the pathological state of water retention in some forms of congestive heart failure.

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Reprint requests to San-e Ishikawa, M.D., Division of Endocrinology and Metabolism, Department of Medicine, Jichi Medical School, 3311-1 Yakushiji Minamikawachi-machi, Tochigi 329-04 Japan.

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